(D)-LIMONENE
CASRN: 5989-27-5

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Best Sections

Ongoing Test Status :
The following link will take the user to the National Toxicology Program (NTP) Test Agent Search Results page, which tabulates all of the "Standard Toxicology & Carcinogenesis Studies", "Developmental Studies", and "Genetic Toxicity Studies" performed with this chemical. Clicking on the "Testing Status" link will take the user to the status (i.e., in review, in progress, in preparation, on test, completed, etc.) and results of all the studies that the NTP has done on this chemical. [http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch.searchresults&searchterm=**5989-27-5**
[Available from: http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch.searchresults&searchterm=5989-27-5 **QC REVIEWED**

Non-Human Toxicity Excerpts :
/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ ... Tumor weight was significantly reduced in **5**-FU group (2.55+/-0.28 g), d-limonene group (1.49+/-0.09 g) and combined treatment group (1.48+/-0.21 g) compared with the control group(2.73+/-0.23 g, P<0.05). In **5**-FU group, d-limonene group, combined treatment group, the inhibition rates were 2.60%,47.58% and 46.84% and 0, respectively; AI was (3.31+/-0.33)%, (8.26+/-1.21)%, (20.99+/-1.84)% and (19.34+/-2.19)%, respectively; MVD was (8.64+/-2.81), (16.77+/-1.39), (**5**.32+/-4.26) and (**5**.86+/-2.**27**), respectively; VEGF expression was (45.77+/-4.79), (41.34+/-**5**.41), (29.71+/-8.92) and (28.24+/-8.55), respectively. The incidences of peritoneal metastasis decreased significantly in **5**-FU group(77.8%), d-limonene group (20.0%) and combined group (22.2%) compared with control group (100%) versus 62.5%,30% and 22.2%) (P<0.05). Liver metastasis was inhibited and the incidences decreased significantly in **5**-FU group, d-limonene group and combined group than that in control group (87.5% vs 55.5%, 20.0% and 22.2% respectively)(P<0.05). The incidence of ascites in control group, **5**-FU group, d-limonene group and combined group was 25.0%, 22.2%, 0, 0, respectively and 12.5%, 11.1% 0, 0, with respect to the metastasis rate to other organs.
[Lu XG et al; World J Gastroenterol 10 (14): 2140-4 (2004)] **PEER REVIEWED** PubMed Abstract

Non-Human Toxicity Excerpts :
/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ Groups of five young adult male F344/N rats each were administered d-limonene at dose levels of 0, 75, 150 or 300 mg/kg bw/d five days a week for **27** days. Observations included daily body weight,

weekly food intake, liver and kidney weights and light microscopy and histology of liver and kidneys. Rats were examined for hyaline droplet formation, granular cast formation and chronic nephrosis. Two-dimensional gel electrophoresis evaluation of protein profiles was conducted on samples of kidneys in the 150 mg/kg dose group killed on day 6. Dose related increases in liver and kidney weights were reported for all dose levels. Renal effects were noted including protein profile changes, hyaline droplet formation, and accumulation of alpha-2-globulin was reported. Chronic nephrosis was present in all kidneys of treated animals killed on day **27**.
[EPA/Office of Pollution Prevention and Toxics; High Production Volume (HPV) Challenge Program's Robust Summaries and Test Plans. Limonen. Available from, as of February 3, 2006: http://www.epa.gov/hpv/pubs/hpvrstp.htm **PEER REVIEWED**

Average Daily Intake :
The intake of d-limonene in food varies due to differing diet patterns. Based on daily US consumption of d-limonene per capita, the intake of d-limonene from food for the general population was estimated to be 0.**27** mg/kg body weight per day(1).
[(1) WHO; International Programme on Chemical Safety Concise International Chemical Assessment Document No. 5. Limonene ISBN 92 4 153005 7 (1998)] **PEER REVIEWED**

Non-Human Toxicity Excerpts :
/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ d-Limonene (purity >99%) was administered by gavage at doses of 0 (corn oil), 413, 825, 1650, 3300 or 6600 mg/kg to **5** F344/N rats and **5** B6C3F1 mice /sex/group for 12 days over a 16 day period (**5** days per week). All high dose rats and **5**/**5** males and 3/**5** female rats at 3300 mg/kg died in two days. Body weight was reduced for surviving 3300 mg/kg females (8%) and 1650 mg/kg male rats (10%). All but one mouse in the 3300 and 6600 mg/kg groups died within three days. Body weights of surviving mice were not affected. No clinical signs or compound related lesions were observed for either species.
[California Environmental Protection Agency/Department of Pesticide Regulation; Toxicology Data Review Summaries. Available from: http://www.cdpr.ca.gov/docs/toxsums/toxsumlist.htm on d-Limonene as of February 2, 2006.] **PEER REVIEWED**

Non-Human Toxicity Excerpts :
/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ Groups of 10 rats of each sex were administered 0, 150, 300, 600, 1200 or 2400 mg/kg bw/day d-limonene in corn oil by gavage once/day, **5** days/wk for 13 weeks. Animals were housed **5** per cage and fed ad libitum. The animals were observed twice/day and weighed once/wk. Necropsies were performed on all animals. Histological examinations were performed on all vehicle control and high dose animals and all female rats in the 1200 mg/kg group. Tissues examined included adrenal glands, brain, colon, esophagus, eyes (if grossly abnormal), femur, sternebrae or vertebrae including marrow, gross lesions and tissue masses with regional lymph nodes, heart kidneys, liver, lungs and mainstem bronchi,

mammary gland, mandibular or mesenteric lymph nodes, pancreas, parathyroids, pituitary gland, prostate/testes or ovaries/uterus, salivary glands, small intestine, spinal cord (if neurologic signs present), spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder. Kidneys were examined for all male rats. 90% of female rats (9/10) and 50% of male rats (**5**/10) receiving 2400 mg/kg bw/day limonene died within the first week of the study. The final mean body weights of male rats receiving the three highest doses (600, 1200 or 2400 mg/kg bw/day) were reported to be 6%, 12%, or 23% lower than that of the controls, respectively. Rough hair coats, lethargy, and excessive lacrimation were observed for all animals at the two highest dose levels. Nephropathy was reported for all groups of male rats but a dose related increase in severity of the lesion was reported for the dosed groups. The nephropathy was characterized by degeneration of epithelium in the convoluted tubules, granular casts with tubular lumens, primarily in the outer stripe of the outer medulla, and regeneration of the tubular epithelium. Hyaline droplets were observed in the epithelium of the proximal convoluted tubules in all groups of male rats including vehicle controls. Upon further review to determine if there were differences in these findings between control and treated animals, the blinded slides revealed no definite differences in the accumulation of hyaline droplets.
[EPA/Office of Pollution Prevention and Toxics; High Production Volume (HPV) Challenge Program's Robust Summaries and Test Plans. Limonen. Available from, as of February 3, 2006: http://www.epa.gov/hpv/pubs/hpvrstp.htm **PEER REVIEWED**

Non-Human Toxicity Excerpts :
/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ Groups of **5**-wk-old male rats received 0, 2, **5**, 10, 30 or 75 mg/kg bw/day d-limonene daily via oral gavage for 13 weeks (**5** days/wk). Rats from selected dose groups were necropsied throughout the study (days 8-29), with all remaining rats necropsied at the end of the study. Rats were observed daily for toxicity signs. Body weights were taken daily. Linear regression analyses indicated increased relative kidney and liver weights at the two highest dose levels. Histological examination revealed changes characterized by hyaline droplet formation, granular casts and multiple cortical changes, all of which was classified as chronic nephrosis. Exacerbation of hyaline droplet formation was reported at the earliest necropsy 8 days after administration at the 10 mg/kg bw/day dose level.
[EPA/Office of Pollution Prevention and Toxics; High Production Volume (HPV) Challenge Program's Robust Summaries and Test Plans. Limonen. Available from, as of February 3, 2006: http://www.epa.gov/hpv/pubs/hpvrstp.htm **PEER REVIEWED**

Atmospheric Concentrations :
URBAN/SUBURBAN: Limonene (unspecified isomer) was detected in 97% of 17 indoor air samples taken at residences in Ruston, WA, 1985-6, at a concn ranging from 1.6 to 78 ug/cu m (mean and median 18 ug/cu m and 11 ug/cu m, respectively), outdoor concns were typically an order of magnitude lower(1). Limonene (unspecified isomer) was identified, not quantified, in 37 indoor and 12 outdoor samples from 36 houses (50 total measurements) in Chicago, IL(2). The concn of limonene (unspecified isomer) in the air

above Moscow Mountain, ID, 1976-1977, ranged from <10 to 50 parts per trillion (3). The mean and maximum concn of limonene (unspecified isomer) in 40 homes in Oak Ridge/Knoxville, TN, 1982-3, was 16 ug/cu m and 77.5 ug/cu m, respectively(4). The concn of limonene (unspecified isomer) in Houston, TX, ranged from not detected to 5.7 ppb(5). d-Limonene was detected indoors in an office building, 1987, at a concn ranging from 43 to 63 ug/cu m(6). Limonene (unspecified isomer) was listed as a compound typically identified in both indoor and outdoor air(7).

[(1) Montgomery DD; Kalman DA; Appl Ind Hyg 4: 17-20 (1989) (2) Jarke FH et al; Ashrae Trans 87: 153-6 (1981) (3) Holdren MW et al; J Geophys Res 84: 5083-8 (1979) (4) Hawthorne AR et al; pp. 574-26 in Spec Meas Monit Non-Criter Contam. Frederick, ER ed. Pittsburgh, PA: APCA (1983) (5) Bertsch W et al; J Chromatog Sci 12: 175-82 (1974) (6) Weschler CJ et al; Am Ind Hyg Assoc J 51: 261-8 (1990) (7) Harrison RM et al; Environ Tech Lett 9: 521-30 (1988)] **PEER REVIEWED**

Environmental Fate :

AQUATIC FATE: Based on a classification scheme(1), an estimated Koc value of 1,300 determined from a structure estimation method(2), indicates that d-limonene is expected to adsorb to suspended solids and sediment in water(SRC). Volatilization from water surfaces is expected(3) based upon an estimated Henry's Law constant of 0.026 atm-cu m/mole(SRC) derived from its vapor pressure, 1.98 mm Hg(4), and water solubility, 13.8 mg/L(5). Volatilization half-lives for a model river and model lake are 1 hour and 5 days, respectively(SRC). According to a classification scheme(6), an estimated BCF of 660(SRC), from a log Kow of 4.57(7), and a regression derived equation(8), suggests the potential for bioconcentration in aquatic organisms is high(SRC). d-Limonene is reported to undergo biodegradation under aerobic conditions, but is resistant to biodegradation under anaerobic conditions(9).

[(1) Swann RL et al; Res Rev 85: 17-28 (1983) (2) Meylan WM et al; Environ Sci Technol 26: 1560-67 (1992) (3) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 4-9, 5-4, 5-10, 15-1 to 15-29 (1990) (4) Yaws CL; Handbook of Vapor Pressure. Vol 3: C8-C28 Compounds. Houston, TX: Gulf Pub Co (1994) (5) Massaldi HA, King CJ; J Chem Eng Data 18: 393-7 (1973) (6) Franke C et al; Chemosphere 29: 1501-14 (1994) (7) Li J, Perdue EM; Physicochemical properties of selected monoterpenes. Preprints of papers presented at the 209th ACS National Meeting Anaheim, CA April 2-7, 35(1): 134-7 (1995) (8) Meylan WM et al; Environ Toxicol Chem 18: 664-72 (1999) (9) WHO; International Programme on Chemical Safety Concise International Chemical Assessment Document No. 5. Limonene ISBN 92 4 153005 7 (1998)] **PEER REVIEWED**

Environmental Abiotic Degradation :

The rate constant for the vapor-phase reaction of d-limonene with photochemically-produced hydroxyl radicals has been measured as 1.71X10-10 cu cm/molecule-sec at 25 deg C(1). This corresponds to an atmospheric half-life of about 2.6 hours at an atmospheric concentration of 5X10+5 hydroxyl radicals per cu cm(1). The rate constant for the vapor-phase reaction of d-limonene with ozone has been measured as 4.42X10-18 cu cm/molecule-sec at 25 deg C(2). This corresponds to an atmospheric half-life of about

37 minutes at an atmospheric concentration of 7X10+11 molecules per cu cm(2). The calculated nighttime lifetime for the reaction of d-limonene with nitrate radicals is 9 minutes(3). Photolysis of d-limonene in the presence of nitrogen oxides produces formaldehyde, formic acid, carbon monoxide, carbon dioxide, acetaldehyde, peroxyacetyl nitrate and acetone(4). Hydrolysis is not expected to be an important environmental fate process for d-limonene since it lacks functional groups that hydrolyze under environmental conditions(**5**).
[(1) Kwok ESC, Atkinson R; Estimation of hydroxyl radical reaction rate constants for gas-phase organic compounds using a structure-reactivity relationship: an update. Riverside, CA: Univ CA, Statewide Air Pollut Res Ctr. CMA Contract No. ARC-8.0-OR (1994) (2) Atkinson R; Chem Rev 85: 69-201 (1985) (3) Winer AM et al; Science 224: 156-9 (1984) (4) Darnall KR et al; Environ Sci Tech 10: 692-6 (1976) (5) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 7-4, 7-5 (1990)] **PEER REVIEWED**

Volatilization from Water/Soil :
The Henry's Law constant for d-limonene is estimated as 0.025 atm-cu m/mole(SRC) derived from its vapor pressure, 1.98 mm Hg(1), and water solubility, 13.8 mg/L(2). This Henry's Law constant indicates that d-limonene is expected to volatilize rapidly from water surfaces. Based on this Henry's Law constant, the volatilization half-life from a model river (1 m deep, flowing 1 m/sec, wind velocity of 3 m/sec)(2) is estimated as approximately 1 hour(SRC). The volatilization half-life from a model lake (1 m deep, flowing 0.05 m/sec, wind velocity of 0.**5** m/sec)(2) is estimated as approximately **5** days(SRC). d-Limonene's Henry's Law constant(SRC) indicates that volatilization from moist soil surfaces may occur(SRC). d-Limonene may volatilize from dry soil surfaces(SRC) based upon its vapor pressure(1).
[(1) Yaws CL; Handbook of Vapor Pressure. Vol 3: C8-C28 Compounds. Houston, TX: Gulf Pub Co (1994) (2) Massaldi HA, King CJ; J Chem Eng Data 18: 393-7 (1973) (3) Lyman WJ et al; Handbook of Chemical Property Estimation Methods NY: McGraw-Hill pp. 15-15 to 15-29 (1982)] **PEER REVIEWED**

Atmospheric Concentrations :
URBAN/SUBURBAN: Limonene (unspecified isomer) was qualitatively detected in the air of Leningrad, Russia 1976, and **5** other Russian cities(1,2). Limonene (unspecified isomer) was detected in suburban air samples in Germany, 1985, at concns ranging from not detected to 2.0 ng/cu m(3,4). Limonene (unspecified isomer) was qualitatively detected in air samples taken at 2 Stockholm preschools, 1981-2(**5**). Limonene (unspecified isomer) was detected in indoor and outdoor air in Northern Italy, 1983-8, at mean concns of 140 ug/cu m and 2 ug/cu m, respectively(6).
[(1) Ioffe BV et al; J Chromatog 142: 787-95 (1977) (2) Ioffe BV et al; Environ Sci Technol 13: 864-9 (1979) (3) Juttner F; Chemosphere 17: 309-17 (1988) (4) Juttner F; Chemosphere 15: 985-92 (1986) (5) Noma E et al; Atmos Environ 22: 451-60 (1988) (6) DeBortoli M et al; Environ Int 12: 343-50 (1986)] **PEER REVIEWED**

U. S. Production :
(1979) MORE THAN 4.5X10+**5** G /UNSPECIFIED ISOMER/
[SRI] **PEER REVIEWED**

Spectral Properties :
Index of refraction: 1.4743 at 21 deg C/D; specific optical rotation: +123.8 deg at 19.**5** deg C/D
[Lide, D.R., G.W.A. Milne (eds.). Handbook of Data on Organic Compounds. Volume I. 3rd ed. CRC Press, Inc. Boca Raton ,FL. 1994., p. V3: 2307] **PEER REVIEWED**

Antidote and Emergency Treatment :
Basic treatment: Establish a patent airway. Suction if necessary. Watch for signs of respiratory insufficiency and assist ventilations if necessary. Administer oxygen by nonrebreather mask at 10 to 15 L/min. Monitor for pulmonary edema and treat if necessary ... . Anticipate seizures and treat if necessary ... . For eye contamination, flush eyes immediately with water. Irrigate each eye continuously with normal saline during transport ... . Do not use emetics. For ingestion, rinse mouth and administer **5** ml/kg up to 200 ml of water for dilution if the patient can swallow, has a strong gag reflex, and does not drool. /Turpentine, terpenes, and related compounds/
[Bronstein, A.C., P.L. Currance; Emergency Care for Hazardous Materials Exposure. 2nd ed. St. Louis, MO. Mosby Lifeline. 1994., p. 212-13] **PEER REVIEWED**

Human Toxicity Excerpts :
/HUMAN EXPOSURE STUDIES/ Patch testing in consecutive dermatitis patients from Sweden and Belgium revealed positive reactions in 1.**5**-2% of the subjects tested with oxidized d-limonene, a finding similar to that observed with other common sensitizers, such as formaldehyde. d-Limonene reduced non-immunological contact urticaria caused by cinnamic aldehyde, with competitive receptor inhibition suggested as the mechanism of suppression. No sensitizing effect was observed when 25 volunteers were exposed to d-limonene in a Human Maximization Test.
[International Programme on Chemical Safety; Concise International Chemical Assessment Documents Number 5: Limonene p.15 (1998). Available from, as of February 3, 2006: http://www.inchem.org/pages/cicads.html **PEER REVIEWED**

Non-Human Toxicity Excerpts :
/LABORATORY ANIMALS: Acute Exposure/ Adult male and female Sprague Dawley rats were given single oral doses of 0, 0.1, 0.3, 1, or 3 mmol d-limonene/kg (0, 14, 41, 136, or 409 mg/kg) in corn oil. A dose response relationship for acute exacerbation of hyaline droplets by d-limonene treatment was observed. Hyaline droplets were graded according to size, eosinophilic intensity, and the number of tubules loaded with droplets. Control rats received a mean score of 3. At 3 mmol/kg, admin of d-limonene resulted in a

score of 10. At 0.1 mmol/kg, no effect on hyaline droplet accumulation was seen in male rats. 24 hr after admin of 3 mmol d-limonene/kg, the renal concentration of d-limonene equivalents was approximately 2.**5** times higher in male rats than in female rats. Equilibrium dialysis in the presence or absence of sodium dodecyl sulfate indicated that approximately 40% of the d-limonene equivalents in male rat kidney associated with proteins in a reversible manner, whereas no significant association was observed between d-limonene equivalents and female rat kidney proteins. Gel filtration HPLC indicated that d-limonene in male rat kidney is associated with a protein fraction having a mol wt of approximately 20,000. Using reverse phase HPLC, d-limonene was shown to be associated with alpha-2u-globulin which was identified by amino acid sequencing. The major metabolite associated with alpha-2u-globulin was d-limonene-1,2-oxide. Parent d-limonene was also identified as a minor component in the alpha-2u-globulin fraction.
[Lehman McKeeman LD et al; Toxicol Appl Pharmacol 99 (2): 250-9 (1989)] **PEER REVIEWED** PubMed Abstract

Non-Human Toxicity Excerpts :
/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ Increases in hepatic cytochrome P-450 content have been observed... in rats administered 5% d-limonene in the diet for 2 weeks. Increased epoxide hydratase activity was observed in rats administered 1% or 5% d-limonene in the diet for 2 weeks. Increases in phase II enzymes (glutathionyltransferase and UDP-glucuronyltransferase) during the exposure of rats to 5% limonene in food have also been described. Increased relative liver weight (from **5** to 20 times) has been observed in rats administered d-limonene at a dose of 75-300 mg/kg body weight; at 300 mg/kg body weight, the increase was significant.
[International Programme on Chemical Safety; Concise International Chemical Assessment Documents Number 5: Limonene p.13 (1998). Available from, as of February 3, 2006: http://www.inchem.org/pages/cicads.html **PEER REVIEWED**

Non-Human Toxicity Excerpts :
/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ d-Limonene is considered a skin irritant. ...In an in vivo study of rabbit skin irritation, d-limonene was ranked 3.**5** of 8 on the basis of the primary irritation index; effects were graded according to OECD Test Guideline 404. In a study in rabbits, d-limonene caused irritation to the eyes.
[International Programme on Chemical Safety; Concise International Chemical Assessment Documents Number 5: Limonene p.12 (1998). Available from, as of February 3, 2006: http://www.inchem.org/pages/cicads.html **PEER REVIEWED**

Non-Human Toxicity Excerpts :
/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ In a 2-year study, d-limonene was administered (/orally/) **5** days/wk to groups of 50 F344/N rats (0, 75, or 150 mg/kg bw/day to males, and 0, 300, or 600 mg/kg bw/day to females) and B6C3F1 mice (0, 250, or 500 mg/kg bw/day to males, and 0, 500, or 1000 mg/kg bw/day to

females). Slightly lower body weights were observed for rats in the high-dose groups and female mice in the high-dose group; however, no clinical symptoms could be related to the administration of d-limonene. For female rats in the high-dose group, survival was reduced after 39 weeks. There was clear evidence of carcinogenic activity of d-limonene in male rats, based upon a dose-related increase in the incidence of hyperplasia and adenoma/ adenocarcinoma in renal tubular cells. However, there was no evidence of carcinogenicity in female rats or in male and female mice. The carcinogenic response in the kidney of male rats has been linked to a unique renal perturbation involving alpha2u-globulin.
[International Programme on Chemical Safety; Concise International Chemical Assessment Documents Number 5: Limonene p.14 (1998). Available from, as of February 3, 2006: http://www.inchem.org/pages/cicads.html
PEER REVIEWED

Non-Human Toxicity Excerpts :
/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ To determine whether d-limonene would cause a sustained increase in renal cell proliferation and exhibit promoting activity for the development of renal adenomas in male F344 rats, the animals were administered (by stomach tube) d-limonene (150 mg/kg bw/day) as a promoter **5** days/wk for 30 weeks. N-ethyl- N-hydroxyethylnitrosamine (500 ppm) was used as an initiator in the drinking-water for 2 weeks. In addition, male alpha2u-globulin-deficient rats were exposed in the same manner to determine if the male rat specific urinary protein alpha2u-globulin is required for d-limonene to cause these effects. Exposure to d-limonene alone caused a significant increase in the number of atypical tubules and atypical hyperplasias in F344 rats, compared with vehicle controls. There was no increase in the incidence of tumors or preneoplastic lesions in the alpha2u-globulin-deficient rats exposed to d-limonene, whereas a 10-fold increase in the incidence of renal adenoma and atypical hyperplasia was observed in F344 rats exposed to d-limonene, compared with controls. There was a significant decrease in the incidence of liver tumors in animals exposed to N-ethyl- N-hydroxyethylnitrosamine and d-limonene, compared with N-ethyl- N-hydroxyethylnitrosamine exposure alone.
[International Programme on Chemical Safety; Concise International Chemical Assessment Documents Number 5: Limonene p.14 (1998). Available from, as of February 3, 2006: http://www.inchem.org/pages/cicads.html
PEER REVIEWED

Non-Human Toxicity Excerpts :
/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ The anticarcinogenic effects of monocyclic monoterpenes such as limonene were demonstrated when given during the initiation phase of 7,12-dimethylbenz(a)anthracene induced mammary cancer in Wistar-Furth rats. The possible mechanisms for this chemoprevention activity including limonene's effects on 7,12-dimethylbenz(a)anthracene-DNA adduct formation and hepatic metabolism of 7,12-dimethylbenz(a)anthracene were investigated. Twenty four hours after carcinogen administration, there were approx 50% decreases in 7,12-dimethylbenz(a)anthracene-DNA adducts found in control animals formed in the liver, spleen, kidney and lung of

limonene fed animals. While circulating levels of 7,12-dimethylbenz(a)anthracene and/or its metabolites were not different in control and limonene fed rats, there was a 2.3 fold increase in 7,12-dimethylbenz(a)anthracene and/or 7,12-dimethylbenz(a)anthracene derived metabolites in the urine of the limonene fed animals. Limonene and sobrerol, a hydroxylated monocyclic monoterpenoid with increased chemoprevention activity, modulated cytochrome p-450 and epoxide hydrolyase activity. The 5% limonene diet increased total cytochrome p-450 to the same extent as phenobarbital treatment, while 1% sobrerol (isoeffective in chemoprevention to 5% limonene) did not. However, both 5% limonene and 1% sobrerol diets greatly increased the levels of microsomal epoxide hydrolyase protein and associated hydrating activities towards benzo(a)pyrene 4,**5**-oxide when compared to control and phenobarbital treatment. These changes also modified the rate and regioselectivity of in vitro microsomal 7,12-dimethylbenz(a)anthracene metabolism when compared to phenobarbital treatment or control. Identification of the specific isoforms of cytochrome p-450 induced by these terpenoids was performed with antibodies to cytochrome p-450 isozymes in Western blot analysis and inhibition studies of microsomal 7,12-dimethylbenz(a)anthracene metabolism. Five per cent limonene was more effective than 1% sobrerol at increasing the levels of members of the cytochrome p-4502B and 2C families but was equally effective at increasing epoxide hydrolyase. Furthermore, both terpenoid diets caused increased formation of the proximate carcinogen, 7,12-dimethylbenz(a)anthracene 3,4-dihydrodiol.
[Maltzman TH et al; Carcinogenesis 12 (11): 2081-7 (1991)] **PEER REVIEWED** PubMed Abstract

Non-Human Toxicity Values :
LD50 Mouse oral **5**.6-6.6 g/kg
[Tsuji M et al; Oyo Yakuri 9 (3): 387 (1975)] **PEER REVIEWED**

Non-Human Toxicity Values :
LD50 Rat oral **5** g/kg bw
[International Programme on Chemical Safety; Concise International Chemical Assessment Documents Number 5: Limonene (1998). Available from, as of February 3, 2006: http://www.inchem.org/pages/cicads.html **PEER REVIEWED**

Non-Human Toxicity Values :
LD50 Rat (female) ip 4.**5** g/kg bw /from table/
[International Programme on Chemical Safety; Concise International Chemical Assessment Documents Number 5: Limonene p.13 (1998). Available from, as of February 3, 2006: http://www.inchem.org/pages/cicads.html **PEER REVIEWED**

Non-Human Toxicity Values :
LD50 Mouse sc >41.**5** g/kg bw /from table/
[International Programme on Chemical Safety; Concise International Chemical Assessment Documents Number 5: Limonene p.13 (1998). Available

from, as of February 3, 2006: http://www.inchem.org/pages/cicads.html **PEER REVIEWED**

Non-Human Toxicity Values :
LD50 Rabbit (New Zealand white) dermal >**5** g/kg bw (24 hr application)
[EPA/Office of Pollution Prevention and Toxics; High Production Volume (HPV) Challenge Program's Robust Summaries and Test Plans. Limonen. Available from, as of February 3, 2006: http://www.epa.gov/hpv/pubs/hpvrstp.htm **PEER REVIEWED**

National Toxicology Program Studies :
Two year studies of d-limonene /more than 99% pure/ were conducted by administering 0, 75, or 150 mg/kg d-limonene in corn oil by gavage to groups of 50 F344/N male rats, **5** days per week for 103 weeks; groups of 50 female F344/N rats were administered 0, 300, or 600 mg/kg. Mean body weights of rats dosed with d-limonene were similar to those of vehicle controls throughout the studies. Survival of the high dose female rats after week 39 and of the vehicle control male rats after week 81 was significantly reduced (survival at week 104--male: vehicle control, 29/50; low dose, 33/50; high dose, 40/50; female: 42/50; 40/50; 26/50). The kidney was confirmed as the primary target organ for chemically related lesions. No lesions were observed in female rats. For males, the nonneoplastic lesions included exacerbation of the age-related nephropathy, linear deposits of mineral in the renal medulla and papilla, and focal hyperplasia of the transitional epithelium overlying the renal papilla. Uncommon tubular cell adenomas and adenocarcinomas of the kidney also occurred in dosed male rats, and this effect was supported by a dose-related increased incidence of tubular cell hyperplasia. ... There was clear evidence of carcinogenic activity of d-limonene for male F344/N rats, as shown by increased incidences of tubular cell hyperplasia, adenomas, and adenocarcinomas of the kidney. There was no evidence of carcinogenic activity of d-limonene for female F344/N rats that received 300 or 600 mg/kg.
[DHHS/NTP; Toxicology and Carcinogenesis Studies of d-Limonene (Gavage Studies) p. 3 (1990) Technical Rpt Series No. 347 NIH Pub No. 90-2802] **PEER REVIEWED**

National Toxicology Program Studies :
Groups of 50 male B6C3F1 mice were administered 0, 250, 500 mg/kg, ... /**5** days per week for 103 weeks/; groups of 50 female B6C3FI mice were administered 0, 500, or 1000 mg/kg. Mean body weights of dosed and vehicle control male mice were similar throughout the studies. Mean body weights of high dose female mice were notably lower than those of the vehicle controls after week 28. Survival of the low dose group-of male mice was significantly lower than that of vehicle controls at the end of the study (33/50; 24/50; 39/50). No difference in survival was observed between vehicle control and dosed female mice (43/50; 44/50; 43/50). ... No chemically related increases in neoplasms were observed. The incidence of neoplasms of the anterior pituitary gland in high dose female mice was lower than that in vehicle controls (adenomas or carcinomas, combined: vehicle control, 12/49; high dose, 2/48). Cells with an abnormal number of nuclei (8/49; 32/50)

and cytomegaly (23/49; 38/50) were observed in the liver of high dose male mice. There was no evidence of carcinogenic activity of d-limonene for male B6C3Fl mice that received 250 or 500 mg/kg. There was no evidence of carcinogenic activity of d-limonene for female B6C3Fl mice that received 500 or 1000 mg/kg.
[DHHS/NTP; Toxicology and Carcinogenesis Studies of d-Limonene (gavage Studies) p. 3 (1990) Technical Rpt Series No. 347 NIH Pub No. 90-2802] **PEER REVIEWED**

Absorption, Distribution & Excretion :
Twelve Long-Evans male rats were administered single topical doses of **5** mg/kg bw 14C-limonene; the treated area was then occluded for 3 hr (2 males) or 6 hr (10 males). Following occlusion, the residual dose was removed and the treated area was re-occluded. Pairs of treated rats were killed at 3, 6, 24, 48, and 72 hr; urine and feces were collected from rats killed at 24, 48, and 72 hr, and plasma and tissue samples were taken at all time points. ...Peak concentrations of radioactivity in tissue samples were measured 3-6 hr after dosing in the gastrointestinal tract (0.1-0.4% dose/g), livers and kidneys (0.08-0.2% dose/g), and thyroid and fat (0.02-0.06% dose/g); except for the gastrointestinal tract, concentrations of radioactivity in all tissues were appreciably lower at 24 hr. After 6 hr of exposure, 48% of the radioactivity was recovered in the skin; at the 24-72 hr sampling times, 8-12% was excreted in urine, 1-3% was excreted in feces, and 14-18% was expired in air. Total mean recovery of radioactivity was reported to be approximately 76%. Following oral administration, the highest concentration of d-limonene or its metabolites in rats was found in the serum fraction of blood after 2 hr. The other major organs containing metabolites of d-limonene were the liver and kidney, with peaks 1-2 hr after ingestion. After 48 hr, negligible amounts of d-limonene metabolites remained in the body. Approximately 60% of d-limonene was excreted in the urine, 5% in the feces, and 2% was expired.
[Joint FAO/WHO Expert Committee on Food Additives; WHO Food Additives Series 30: Limonene (1993). Available from, as of February 3, 2006: http://www.inchem.org/documents/jecfa/jecmono/v30je05.htm **PEER REVIEWED**

Absorption, Distribution & Excretion :
In a phase I clinical trial of orally administered d-limonene, 17 women and 15 men aged 35-78 (median, 57), with advanced metastatic solid tumors received an average of three treatment cycles of 21 days (one dose on day 1, then three daily doses on days 4-21) at doses ranging from 0.**5** to 12 g/sq m body surface area. d-Limonene was slowly absorbed, the maximal plasma concentration being attained at 1-6 hr. The mean peak plasma concentrations of d-limonene were 11-20 umol/L, and the predominant metabolites were perillic acid (21-71 umol/L), dihydroperillic acid (17-28 �mol/L), limonene-1,2-diol (10-21 umol/L), uroterpinol (14-45 umol/L) and an isomer of perillic acid. After reaching these peaks, the plasma concentrations decreased according to first-order kinetics. The values for the integrated area under the curve for time-concentration showed little variation with administered dose. There was no accumulation of the parent or metabolites after a treatment cycle.
[IARC. Monographs on the Evaluation of the Carcinogenic Risk of

Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work). Available at: http://monographs.iarc.fr/index.php p. V73 311 (1999)] **PEER REVIEWED**

Absorption, Distribution & Excretion :

... Plasma concentrations of perillic acid reached maximal levels at 1 h after the lemonade consumption and declined rapidly as a function of time with the terminal elimination half-life ranging from 0.82 to 1.84 h. The maximum plasma perillic acid concentration ranged from 2.08 to 13.98 micro M, and the levels were undetectable at 24 h after the lemonade consumption. The area under the plasma concentration-time curves of perillic acid ranged from **5**.07 to 32.59 (micro M) x h.

[Chow HH et al; Cancer Epidemiol Biomarkers Prev 11 911): 1472-6 (2002)] **PEER REVIEWED** PubMed Abstract

Metabolism/Metabolites :

After oral administration of (14)C-labeled d-limonene, **5** new metabolites were isolated from dog and rat urine: 2-hydroxy-p-menth-8-en-7-oic acid, perillylglycine, perillyl-beta-d-glucopyranosiduronic acid, p-mentha-1,8-dien-6-ol, and probably p-menth-1-ene-6,8,9-triol.

[Kodama R et al; Xenobiotica 6 (6): 377 (1976)] **PEER REVIEWED** PubMed Abstract

Metabolism/Metabolites :

A pilot study was conducted in healthy volunteers (**5** women, 2 men) to investigate the metabolism and the toxicity of pharmacologically (supradietary) administered d-limonene. After the subjects had ingested 100 mg/kg d-limonene in a custard, their blood was drawn at 0 and 24 hr for blood chemistry and at 0, 4 and 24 hr for analysis of metabolites. Gas chromatography�mass spectrometry indicated the presence of five d-limonene metabolites in plasma: two major peaks were identified as dihydroperillic acid and perillic acid and a third major peak was limonene-1,2-diol; limonene itself was only a minor component. Two minor peaks were found to be the respective methyl esters of the acids. In all subjects, the metabolite concentrations were higher at 4 hr than at 24 hr, but a half-life value was not determined.

[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work). Available at: http://monographs.iarc.fr/index.php p. V73 310 (1999)] **PEER REVIEWED**

Mechanism of Action :

The mechanism by which d-limonene causes alpha2u-globulin accumulation in the male rat kidney has been elucidated. The prerequisite step in the development of the nephropathy is the binding to alpha2u-globulin of an agent, which in the case of d-limonene is the 1,2-epoxide. This binding is specific for alpha2u-globulin and reversible,

with a binding affinity (Kd) of approximately 5.6X10-7 mol/L. Binding of this ligand to alpha2u-globulin reduces the rate of its lysosomal degradation relative to that of native protein, thereby causing it to accumulate. Lysosomal cathepsin activity towards other protein substrates is not altered. Whereas accumulation of alpha2u-globulin can be observed after a single oral dose of d-limonene, continued treatment results in additional histological changes in the kidney. Phagolysosomes become enlarged, engorged with protein and show polyangular crystalloid inclusions. After 3-4 weeks of dosing, progressive renal injury, characterized by single-cell degeneration and necrosis in the P2 segment of the renal proximal tubule, is noted. Dead cells are sloughed into the lumen of the nephron, contributing to the development of granular casts at the cortico-medullary junction. Renal functional perturbations, including reduced uptake of organic anions, cations and amino acids and mild proteinuria resulting from a large increase in the amount of alpha2u-globulin excreted in urine, are observed. These functional changes occur only in male rats and only at doses that exacerbate the protein droplet formation. In response to the cell death and functional changes, there is a compensatory increase in cell proliferation in the kidney, most notably in the P2 segment of the proximal tubules, the site of protein accumulation. With continued treatment, the cell proliferation persists, but it does not restore renal function. The increase in cell proliferation is linked to the development of renal tubular tumors. alpha2u-Globulin nephropathy and renal-cell proliferation occur at doses consistent with those that produce renal tubular tumors.
[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work). Available at: http://monographs.iarc.fr/index.php p. V73 319 (1999)]
PEER REVIEWED

Mechanism of Action :
In the male rat, the production of renal tumors by chemicals inducing alpha2u-globulin accumulation (CIGA) is preceded by the renal lesions ascribed to alpha2u-globulin-associated nephropathy. The involvement of hyaline droplet accumulation in the early nephrotoxicity associated with CIGA is a major difference from the sequence seen for classical carcinogens. The pathologic changes that precede the proliferative sequence for classical renal carcinogens also include a form of early nephrotoxicity, but no apparent hyaline droplet accumulation. Investigations performed in multiple laboratories ... have demonstrated a consistent association between hyaline droplets containing alpha2u-globulin and production of certain lesions in the male rat kidney. These renal lesions are not found in mice, female rats, or other laboratory species tested. The histopathological sequence in the male rat consists of the following: (1) an excessive accumulation of hyaline droplets containing alpha2u-globulin in renal proximal tubules; (2) subsequent cytotoxicity and single-cell necrosis of the tubule epithelium; (3) sustained regenerative tubule cell proliferation, providing exposure continues; (4) development of intralumenal granular casts from sloughed cell debris associated with tubule dilation, and papillary mineralization; (5) foci of tubule hyperplasia in the convoluted proximal tubules; and finally, (6) renal tubule tumors. Biochemical studies with model compounds show that CIGA or their metabolites bind specifically. but reversibly, to male rat alpha2u-globulin. The resulting alpha2u-globulin-CIGA complex appears to be more resistant to hydrolytic

degradation by lysosomal enzyemes than native, unbound alpha2u-globulin. Inhibition of the catabolism of alpha2u-globulin, a protein only slowly hydrolyzed by renal lysosomal enzymes under normal physiological conditions, provides a plausible basis for the initial stage of protein overload in the nephropathy sequence.
[EPA Risk Assessment Forum; Alpha2u-Globulin: Association with Chemically Induced Renal TOxicity and Neoplasia in the Male Rat. US Environmenal Protection Agency (1991) EPA/625/3-91/019F] **PEER REVIEWED**

Interactions :
Mouse mammary glands respond to carcinogen stimulus to form mammary lesions in organ culture. In this study it was determined whether the effective chemopreventive agents are active against initiation or the promotion phase of lesion development. Mammary glands were subjected to 24 hr exposure to 2 mg/ml dimethylbenz(a)anthracene followed by a **5** day exposure to 7,12-tetradecanoyl phorbol-13-acetate. This treatment protocol allows the study of initiation and promotion aspects of lesion development. Chemopreventive agents effective when present prior to the carcinogen were considered as anti-initiators, whereas agents effective when present after the dimethylbenz(a)anthracene treatment along with 7,12-tetradecanoyl pherbol-13-acetate were considered as anti-promoters. Within the chemopreventive agents evaluated limonene was an anti-initiator.
[Mehta RG, Moon RC; Anticancer Res 11 (2): 593-6 (1991)] **PEER REVIEWED** PubMed Abstract

Interactions :
The monoterpene d-limonene has been shown to an effective, non-toxic chemopreventive agent in mammary and other rodent tumor models. The studies reported here investigated structure activity relationships among limonene and three hydroxylated derivatives in the prevention of dimethylbenz[a]anthracene induced mammary cancer. Rats were fed control or 1% limonene, carveol, uroterpenol or sobrerol diets from 2 wk before to one week after carcinogen administration. Carveol, uroterpenol and sobrerol significantly prolonged tumor latency and decreased tumor yield. Sobrerol was the most potent of the monoterpenes tested, decreasing tumor yield to half that of the control, a level previously achieved with 5% limonene diets. Excretion of radioactivity from (3)H dimethylbenz(a)anthracene was doubled in rats fed 5% limonene and nearly tripled in rats fed 1% sobrerol. Sobrerol is thus **5** fold more potent than limonene in both enhancing carcinogen excretion and in preventing tumor formation. These data demonstrate that hydroxylation of monoterpenes affects chemopreventive potential, with 2 hydroxyl groups greater than 1 greater than 0. Sobrerol, carveol and uroterpenol are novel cancer chemopreventive agents with little or no toxicity.
[Crowell PL et al; Carcinogenesis 13 (7): 1261-4 (1992)] **PEER REVIEWED** PubMed Abstract

Interactions :
The anticarcinogenic effects of monocyclic monoterpenes such as limonene were

demonstrated when given during the initiation phase of 7,12-dimethylbenz(a)anthracene induced mammary cancer in Wistar-Furth rats. The possible mechanisms for this chemoprevention activity including limonene's effects on 7,12-dimethylbenz(a)anthracene-DNA adduct formation and hepatic metabolism of 7,12-dimethylbenz(a)anthracene were investigated. Twenty four hours after carcinogen administration, there were approx 50% decreases in 7,12-dimethylbenz(a)anthracene-DNA adducts found in control animals formed in the liver, spleen, kidney and lung of limonene fed animals. While circulating levels of 7,12-dimethylbenz(a)anthracene and/or its metabolites were not different in control and limonene fed rats, there was a 2.3 fold increase in 7,12-dimethylbenz(a)anthracene and/or 7,12-dimethylbenz(a)anthracene derived metabolites in the urine of the limonene fed animals. Limonene and sobrerol, a hydroxylated monocyclic monoterpenoid with increased chemoprevention activity, modulated cytochrome p-450 and epoxide hydrolyase activity. The 5% limonene diet increased total cytochrome p-450 to the same extent as phenobarbital treatment, while 1% sobrerol (isoeffective in chemoprevention to 5% limonene) did not. However, both 5% limonene and 1% sobrerol diets greatly increased the levels of microsomal epoxide hydrolyase protein and associated hydrating activities towards benzo(a)pyrene 4,**5**-oxide when compared to control and phenobarbital treatment. These changes also modified the rate and regioselectivity of in vitro microsomal 7,12-dimethylbenz(a)anthracene metabolism when compared to phenobarbital treatment or control. Identification of the specific isoforms of cytochrome p-450 induced by these terpenoids was performed with antibodies to cytochrome p-450 isozymes in Western blot analysis and inhibition studies of microsomal 7,12-dimethylbenz(a)anthracene metabolism. Five per cent limonene was more effective than 1% sobrerol at increasing the levels of members of the cytochrome p-4502B and 2C families but was equally effective at increasing epoxide hydrolyase. Furthermore, both terpenoid diets caused increased formation of the proximate carcinogen, 7,12-dimethylbenz(a)anthracene 3,4-dihydrodiol.
[Maltzman TH et al; Carcinogenesis 12 (11): 2081-7 (1991)] **PEER REVIEWED** PubMed Abstract

Environmental Fate/Exposure Summary :
d-Limonene's production and use in flavorings, fragrances, cosmetics, as a solvent, wetting agent and in the manufacture of resins may result in its release to the environment through various waste streams. d-Limonene is used as both an active and inert ingredient in pesticides. Its use as an insecticide, insect repellant, and animal (dog and cat) repellant, will result in its direct release to the environment. d-Limonene is found in many oils and fruits and is emitted to the environment from plants and the combustion of wood. If released to air, a vapor pressure of 1.98 mm Hg at 25 deg C indicates d-limonene will exist solely in the vapor-phase in the ambient atmosphere. Vapor-phase d-limonene is degraded rapidly in the atmosphere by reaction with photochemically-produced hydroxyl radicals, nitrate radicals and ozone. The half-lives for these reactions are very short, ranging from several minutes to about 2.6 hours. If released to soil, d-limonene is expected to have low mobility based upon an estimated Koc of 1,300. Volatilization from moist soil surfaces is expected to occur given an estimated Henry's Law constant of 0.026 atm-cu m/mole. Volatilization from dry soil surfaces may also occur given the vapor pressure of d-limonene. d-Limonene is reported to undergo

biodegradation under aerobic conditions, but is resistant to biodegradation under anaerobic conditions. If released to water, d-limonene is expected to adsorb to suspended solids and sediment in the water column based upon the Koc data. Volatilization from water surfaces is expected to occur rapidly based upon the estimated Henry's Law constant. Estimated volatilization half-lives for a model river and model lake are 1 hour and **5** days, respectively. d-Limonene is not expected to undergo hydrolysis since it lacks functional groups that hydrolyze under environmental conditions. An estimated BCF of 660 suggests the potential for bioconcentration in aquatic organisms is high. Occupational exposure to d-limonene may occur by inhalation or dermal contact during its production, formulation, transport or use. Exposure to the general population may occur through inhalation of ambient air, ingestion of food, and dermal contact with consumer products containing d-limonene. d-Limonene is an active ingredient in several registered shampoo, dip and spray products applied to domestic animals to control fleas and ticks and human exposure to d-limonene can occur for the general population or veterinary professionals that use these products. (SRC)
PEER REVIEWED

Natural Pollution Sources :
d-Limonene is found in many oils and fruits including orange, lemon, grapefruit, berry, leaf, caraway, dill, bergamot, peppermint and spearmint oils(1-4). d-Limonene emissions to the environment are associated with wax myrtle, sweet acacia, oranges, tomatoes, grasses, and California western sagebrush(**5**). Emissions are also associated with balsam poplar, European larche, European fir, Scots pine, Siberian pine, silver fir, common juniper, zeravshan juniper, pencil cedar, evergreen cypress, northern white cedar, chinese arbor vitae, marsh tea and deciduous moss(6).
[(1) Rogers JA Jr; in Kirk Othmer Encycl Chem Tech, 3rd ed. NY, NY: Wiley 16: 307-32 (1981) (2) Bauer K et al; in Ullmann's Encycl Indust Tech, 5th ed. Gerhartz W et al, eds. VCH Publ A11: 141 (1988) (3) O'Neil MJ, ed; Merck Index, 13th ed, Whitehouse Station, NJ Merck & Co. p 984 (2001) (4) Lewis RJ; Hawley's Condensed Chemical Dictionary. 14th ed. NY, NY: Van Nostrand Reinhold Co., p. 669 (2001) (5) Altshuller AP; Atmos Environ 17: 2131-65 (1983) (6) Isidorov VA et al; Atmos Environ 19: 1-8 (1985)] **PEER REVIEWED**

Environmental Fate :
TERRESTRIAL FATE: Based on a classification scheme(1), an estimated Koc value of 1,300 determined from a structure estimation method(2), indicates that d-limonene is expected to have low mobility in soil(SRC). Volatilization from moist soil surfaces is expected to occur based on an estimated Henry's Law constant of 0.026 atm-cu m/mole(SRC) derived from its vapor pressure, 1.98 mm Hg(3), and water solubility, 13.8 mg/L(4). Volatilization from dry soil surfaces may occur given the vapor pressure of this compound(3). d-Limonene is reported to undergo biodegradation under aerobic conditions, but is resistant to biodegradation under anaerobic conditions(**5**). Terpene acclimated inocula prepared from soil obtained from a coniferous forest and hardwood forest in North Carolina degraded limonene with a half-life of approximately 9-20 hours at 23 deg C following a lag period of 15-23 hours(6).

[(1) Swann RL et al; Res Rev 85: 17-28 (1983) (2) Meylan WM et al; Environ Sci Technol 26: 1560-67 (1992) (3) Yaws CL; Handbook of Vapor Pressure. Vol 3: C8-C28 Compounds. Houston,TX: Gulf Pub Co (1994) (4) Massaldi HA, King CJ; J Chem Eng Data 18: 393-7 (1973) (5) WHO; International Programme on Chemical Safety Concise International Chemical Assessment Document No. 5. Limonene ISBN 92 4 153005 7 (1998) (6) Misra G et al; Appl Microbiol Biotechnol 45: 831-838 (1996)] **PEER REVIEWED**

Environmental Fate :

ATMOSPHERIC FATE: According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere(1), d-limonene, which has a vapor pressure of 1.98 mm Hg at 25 deg C(2), is expected to exist solely as a vapor in the ambient atmosphere. Vapor-phase d-limonene is degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals, nitrate radicals and ozone(SRC). The half-life for the reaction with hydroxyl radicals is estimated to be 2.6 hours(SRC) from its rate constant of 1.71X10-10 cu cm/molecule-sec at 25 deg C(3). The half-life for the reaction with ozone is estimated to be 37 minutes(SRC) from its rate constant of 4.42X10-18 cu cm/molecule-sec(4). The calculated nighttime lifetime for the reaction of d-limonene with nitrate radicals is 9 minutes(**5**).

[(1) Bidleman TF; Environ Sci Technol 22: 361-367 (1988) (2) Yaws CL; Handbook of Vapor Pressure. Vol 3: C8-C28 Compounds. Houston,TX: Gulf Pub Co (1994) (3) Kwok ESC, Atkinson R; Estimation of hydroxyl radical reaction rate constants for gas-phase organic compounds using a structure-reactivity relationship: an update. Riverside, CA: Univ CA, Statewide Air Pollut Res Ctr. CMA Contract No. ARC-8.0-OR (1994) (4) Atkinson R; Chem Rev 85: 69-201 (1985) (5) Winer AM et al; Science 224: 156-9 (1984)] **PEER REVIEWED**

Effluent Concentrations :

Limonene (unspecified isomer) was detected as a component of landfill gases from sites in the UK at measured concns of 21-84 mg/cu m in probes buried underground and 7.4 mg/cu m at above ground vents(1). Limonene (unspecified isomer) was qualitatively detected in 2 of 46 U.S. industrial effluent samples(2). Limonene (unspecified isomer) was detected in 6 of 7 samples of kraft pulp mill wastewater at concns ranging from 10-220 ppb in 2 Canadian mills monitored in 1973(3). Limonene (unspecified isomer) was identified, not quantified, in landfill leachate(4). Limonene (unspecified isomer) was qualitatively identified in the effluent gas from refuse waste obtained from a food center in an experiment designed to determine the gases emitted from decaying waste matter at refuse sites, landfills, and trash transfer sites(**5**). Limonene has been associated with effluent from the following industries: extraction of pine gum, paper and pulp mills, plastics materials-synthetic resins and non-vulcanizable elastomers, perfumes, cosmetics and other toilet preparations, organic solvents and lubricating oils and greases(6). Limonene (unspecified isomer) was identified, not quantified, in the emissions of wood burning fireplaces(7).

[(1) Young P, Parker A; pp. 24-41 Hazardous and Industrial Waste Management and Testing 3rd Symp Amer Soc Test Mater (1984) (2) Bursey JT, Pellizzari ED; Analysis of Industrial Wastewater for Organic

Pollutants in Consent Degree Survey. Res Triangle Park, NC: USEPA (1982) (3) Wilson D, Hrutfiord B; Pulp and Paper Canada 76: 91-3 (1975) (4) Venkataramani ES, Ahlert RC; J Water Purif Contr Fed 56: 1178-84 (1984) (5) Koe LC, Ng WJ; Water, Air Soil Pollut 33: 199-204 (1987) (6) Abrams EF et al; Identification of Organic Compounds in Effluents from Industrial Sources Washington, DC: USEPA-560/3-75-002 (1975) (7) Purvis CR et al; Environ Sci Technol 34: 1653-1658 (2000)] **PEER REVIEWED**

Atmospheric Concentrations :

RURAL/REMOTE: The concentrations of limonene and other monoterpenes in air vary considerably. Recorded concentrations in rural areas depend on many factors, such as the type of vegetation, temperature, time of the day, and time of the year(1). The concn of d-limonene in the air over a forest in the Republic of Georgia, July, 1979, ranged from <0.1 to 0.2 ppb(2). The concn of limonene (unspecified isomer) 1.7 m above a maple forest in Quebec ranged from approximately 100 to 1750 parts per trillion over a two day period in June, 1989(3). Limonene (unspecified isomer) was detected in forest air samples in Southern Black Forest region, Germany, 1985, at concns ranging from 1.0 to 89 ng/cu m(4,**5**). Traces of limonene (unspecified isomer) were found in the air over the Landes Forest, France, 1984, which consists mainly of maritime pines(6). The average concn of d-limonene at rural locations in the Rocky Mountains was 0.030 ppb (day) and 0.072 ppb (nighttime)(7).

[(1) WHO; International Programme on Chemical Safety Concise International Chemical Assessment Document No. 5. Limonene ISBN 92 4 153005 7 (1998)(2) Shaw RWJR et al; Environ Sci Tech 17: 389-95 (1983) (3) Clement B et al; Atmos Environ 24A: 2513-6 (1990) (4) Juttner F; Chemosphere 17: 309-17 (1988) (5) Juttner F; Chemosphere 15: 985-92 (1986) (6) Riba ML et al; Atmos Environ 21: 191-3 (1987) (7) Roberts JM et al; Environ Sci Technol 19: 364-369 (1985)] **PEER REVIEWED**

Food Survey Values :

Limonene (unspecified isomer) has been identified as a volatile component of fried chicken(1), chickpea seed(2), orange juice essence(3), mangos(4), roasted filberts(**5**), Beaufort (Gruyere) cheese(6) and baked potatoes(7). It has been detected in a headspace analysis of intact, tree ripened nectarines, but not in an analysis of the blended fruit(8).

[(1) Tang J et al; J Agric Food Chem 31: 1287-92 (1983) (2) Rembold H et al; J Agric Food Chem 37: 659-62 (1989) (3) Moshonas MG, Shaw PE; J Agric Food Chem 38: 2181-4 (1990) (4) MacLeod AJ, Snyder CH; J Agric Food Chem 36: 137-9 (1988) (5) Kinlin TE et al; J Agr Food Chem 20: 1021-8 (1972) (6) Dumont JP, Adda J; J Agr Food Chem 26: 364-7 (1978) (7) Coleman EC et al; J Agric Food Chem 29: 42-8 (1981) (8) Takeoka GR et al; J Agric Food Chem 36: 553-60 (1988)] **PEER REVIEWED**

Emergency Medical Treatment :

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The following Overview, *** LIMONENE ***, is relevant for this HSDB record chemical.

Life Support:

- This overview assumes that basic life support measures have been instituted.

Clinical Effects:

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0.2.1 SUMMARY OF EXPOSURE
 0.2.1.1 ACUTE EXPOSURE
   A)  HUMAN
    1)  Limonene is most likely of low toxicity. Mild dermal
        irritation and skin sensitization may occur. Hematuria
        and albuminuria might occur if large amounts are
        ingested.
    2)  Other symptoms following limonene ingestion may
        include: burning pain in the mouth and throat,
        abdominal pain, nausea, vomiting, diarrhea, transient
        excitement, ataxia, delirium, stupor, coughing,
        choking, dyspnea, cyanosis, fever and tachycardia.
    3)  In addition, pulmonary edema and pneumonitis may occur
        with limonene aspiration or systemic absorption.
        Dizziness and suffocation may be observed following
        limonene inhalation.
   B)  ANIMAL
    1)  MICE - Somnolence and hypothermia have been noted in
        mice. Gastric epithelial irritation was caused by oral
        administration in mice.
    2)  CATS completely wetted with a limonene-containing
        insecticidal dip developed skin excoriation,
        hypersalivation, transient blepharospasm in directly
        exposed eyes, hypothermia, muscle tremors, and ataxia.
0.2.3 VITAL SIGNS
0.2.10 GENITOURINARY
 0.2.10.1 ACUTE EXPOSURE
   A)  Hematuria and albuminuria might occur.
0.2.14 DERMATOLOGIC
 0.2.14.1 ACUTE EXPOSURE
   A)  Dermal irritation and sensitization may occur.
       Percutaneous absorption may occur.
0.2.21 CARCINOGENICITY
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0.2.21.1 IARC CATEGORY

A) IARC Carcinogenicity Ratings for CAS5989-**27-5** (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2006; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2007; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2010; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2010a; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2008; IARC, 2004):
  1) IARC Classification
    a) Listed as: d-Limonene
    b) Carcinogen Rating: 3
      1) The agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans. This category is used most commonly for agents, mixtures and exposure circumstances for which the evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals. Exceptionally, agents (mixtures) for which the evidence of carcinogenicity is inadequate in humans but sufficient in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans. Agents, mixtures and exposure circumstances that do not fall into any other group are also placed in this category.

B) IARC Carcinogenicity Ratings for CAS138-86-3 (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2006; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2007; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2010; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2010a; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2008; IARC, 2004):
  1) Not Listed

Laboratory:

A) Monitor urinalysis, urine output, and renal function tests in patients with significant exposure.

Treatment Overview:

0.4.2 ORAL EXPOSURE

A) Carefully observe patients for the development of any systemic signs or symptoms and administer symptomatic treatment as necessary.

B) ACTIVATED CHARCOAL: Administer charcoal as a slurry (240 mL water/30 g charcoal). Usual dose: 25 to 100 g in adults/adolescents, 25 to 50 g in children (1 to 12 years), and 1 g/kg in infants less than 1 year old.

C) GASTRIC LAVAGE: Consider after ingestion of a potentially life-threatening amount of poison if it can be performed soon after ingestion (generally within 1 hour). Protect airway by placement in Trendelenburg and left lateral decubitus position or by endotracheal intubation. Control any seizures first.

1) CONTRAINDICATIONS: Loss of airway protective reflexes or decreased level of consciousness in unintubated patients; following ingestion of corrosives; hydrocarbons (high aspiration potential); patients at risk of hemorrhage or gastrointestinal perforation; and trivial or non-toxic ingestion.

D) DILUTION: Immediately dilute with 4 to 8 ounces (120 to 240 mL) of water or milk (not to exceed 4 ounces/120 mL in a child).

E) Observe patients with ingestion carefully for the possible development of esophageal or gastrointestinal tract irritation or burns. If signs or symptoms of esophageal irritation or burns are present, consider endoscopy to determine the extent of injury.

0.4.3 INHALATION EXPOSURE

A) INHALATION: Move patient to fresh air. Monitor for respiratory distress. If cough or difficulty breathing develops, evaluate for respiratory tract irritation, bronchitis, or pneumonitis. Administer oxygen and assist ventilation as required. Treat bronchospasm with inhaled beta2 agonist and oral or parenteral corticosteroids.

B) If aspiration occurs, monitor temperature, WBC, arterial blood gases, and chest x-ray. Administer oxygen as required.

0.4.4 EYE EXPOSURE

A) DECONTAMINATION: Irrigate exposed eyes with copious amounts of room temperature water for at least 15 minutes. If irritation, pain, swelling, lacrimation, or photophobia persist, the patient should be seen in a health care facility.

0.4.5 DERMAL EXPOSURE

A) OVERVIEW

1) DECONTAMINATION: Remove contaminated clothing and wash exposed area thoroughly with soap and water. A physician may need to examine the area if irritation or pain persists.

2) Treat dermal irritation or burns with standard topical therapy. Patients developing dermal hypersensitivity reactions may require treatment with systemic or topical corticosteroids or antihistamines.

3) Some chemicals can produce systemic poisoning by absorption through intact skin. Carefully observe patients with dermal exposure for the development of any systemic signs or symptoms and administer symptomatic treatment as necessary.

Range of Toxicity:

A) The minimum lethal human exposure to this agent has not been reported; however, a probable oral lethal dose is 0.**5** to **5** grams/kilogram or between one ounce and one pint in a 70 kg human.

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